

invention as set forth in claims 1-21 of United States Patent No. 4,711,955." In order to obviate this rejection, applicants intend to file a terminal disclaimer upon allowance the withdrawal of the remaining claim rejections in this application.

Claims 101-103, 110-112, 138-139 and 146-151 stand rejected and the specification objected to, under 35 U.S.C. § 112, first paragraph as "failing to provide an enabling disclosure." The Examiner contends that no embodiments in the instant specification which describe how the attachment of labels to the 8-position of purines or to the 7-position of a deazapurine is executed. Applicants traverse this.

The specification need not detail specifics regarding the attachment of the linker arm to the 8-position of a purine because that reaction is a conventional nucleophilic addition reaction known to those skilled in the art as of the filing date of this application. Similarly, processes for attachment of the linker arm to the 7-position of a deazapurine were also known to those of skill of the art at the time of the filing of this application. Applicants' invention relates to what is being attached to the nucleotide to produce the resulting compositions claimed in this application, not to the conventional procedure for making the attachment. Accordingly, the claims are fully enabled.

The disclosure stands objected to on the basis of various purported informalities. In particular, the Examiner has requested that applicants submit replacement pages 1-3 of paper no. 3, amendment B. In response to this objection, applicants have submitted these replacement pages herewith.

Claims 101-103, 110-112, 138, 139 and 146-151 stand rejected under 35 U.S.C. § 112, first and second paragraphs, "as

the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants address below each particular contention of the Examiner corresponding to this rejection as set forth on pages 5-8 of the June 20, 1990 Office Action.

The Examiner contends that the terms "purine", "deazapurine" and "pyrimidine" in claims 101 and 110 are "unduly broad and indefinite." The Examiner has requested applicants limit the scope of the instant claims to the specific embodiments. Applicants traverse this contention.

Applicants' invention relates to the addition of various moieties -- A -- directly or through a linker, to a nucleotide containing a purine, pyrimidine or 7-deazapurine moiety. As of the filing date of this application, it would have been apparent to one skilled in the art that the analogous compounds could be produced using analogous starting materials. As set forth in, e.g., In re Gardner, 427 F.2d 786, 166 USPQ 138, 140 (CCPA 1970), the wide breath of a claim is not objectionable if the specification provides clear basis for the broad scope. Further, the Examiner has not cited any authority nor established a prima facie case for the proposition that the broad disclosure of "purine", "deazapurine" and "pyrimidine" is "unduly broad and indefinite."

The Examiner contends that in claims 101 and 110 "the use of the 7-position in apparent reliance on the purine ring numbering scheme is incorrect" and "that applicant is actually referring to the 5-position". The Examiner also asserts that "similar criticism applies to claims directed to attachment of

sugar moieties to N-9 of a deazapurine. In the case of pyrrolo[2,3-d]pyrimidines the corresponding location is -- position 7 --." Applicants traverse these assertions.

Applicants are unsure of the correctness of the Examiner's position regarding the numbering of the ring structures. Nevertheless, in this application, and as correctly surmised by the Examiner, the term "7-position" is used in reliance on the purine ring numbering scheme, as also is the case with the reference to "N-9". In view of this reliance, applicants are reviewing how, if necessary, to rename the claimed structures.

The Examiner contends that the term "A represents a component of a detectable complex", in claims 101 and 110, the term "a moiety which can be detected", in claims 102 and 111, the term "detectable by means inherent in the polypeptide or by means of detectable moieties which are attached thereto" in claim 149 , the term "a detectable moiety" in the claim 150 and the term "detectable" in the claim 151 "broad and indefinite" or "indefinite and unenabled." Applicants traverse this contention.

The objected to terms are definite, enabled and not overly broad. For example, the term "detection" appears in the specification generally at page 9, lines 28 et seq. And page 10, lines 33 et seq. of this application provide that the moiety "A" should be capable of forming a detectable complex with a polypeptide when the nucleotide containing the moiety "A" as modified in accordance with applicants' teaching, is incorporated into a double-stranded duplex containing either deoxyribonucleic or ribonucleic acid. Thus, the specification refers to complexes of "A", a moiety of at least 3 carbon atoms,

with a polypeptide which complexes are capable of being detected.

Examples of illustrative indicator molecules are listed in the specification, at page 2, lines 9 et seq. florescent dyes, electron-dense reagents and enzymes capable of depositing insoluble reaction products (precipitates). These indicator molecules, when complexed with moiety A and polypeptide, comprise the "detectable complexes" recited in the claims. Not only are these several types of detectable complexes listed, but each is further exemplified by recited complexes. See application page 2, lines 18 et seq.

Applicants have both defined and exemplified species and genera of detectable complexes and moieties suitable for use as component thereof. And applicants have provided a functional definition that would enable one skilled in the art to reproduce their teaching. See In re Gardner, supra. Multiple examples are provided. See, e.g., application p. 12, line 1 - p. 13, line 8; p. 27, line 27 - p. 29, line 10. Moreover, even absent such a listing, the concept of a "detectable moiety" was well known in the art as of the filing date of this application. For all these reasons, applicants believe that the objected-to terms satisfy 35 U.S.C. § 112.

The Examiner also contends that in claims 101 and 110 applicants fail to "further define what is intended by the term 'detectable complex' in a manner commensurate with the implicit limitations of the instant disclosure".

Applicants agree that the claims can only be read in light of the specification which, as demonstrated above, is well-defined in the specification.

The Examiner also contends that applicants "fail to further define the upper limit on the size of 'A'". Applicants

believe they have so fully defined A by type, by example, and by function that they have met the statutory requirement of definiteness. See, e.g., application p. 10, lines 35 et seq. and p. 12 lines 1 et seq. Applicants provide a functional definition and a structural definition of "A" ("at least three carbon atoms"). See, e.g., application p. 12, lines 7 et seq. Applicants disclose generic and specific examples. Preferred examples are disclosed at page 13, lines 1 et seq. In view of such disclosure, one skilled in the art would recognize the metes and bounds of what is claimed.

The Examiner contends that in claims 101 and 110 "the term 'attached to the 8-position of the purine' implies enabling embodiments in the instant disclosure which are not present thus rendering the term both indefinite and unenabled." Applicants traverse the rejection of claims 101 and 110 for the reasons already advanced in response to the § 112, first paragraph rejection regarding attachment of labels to the 8-position of purines. Briefly, means for effecting that attachment were conventional in the art as of the filing date of this application.

The Examiner also contends in claims 101 and 110 the term "at least one" lacks an "upper bound." Applicants traverse this contention.

Although claims 101 and 110 do not specifically recite an upper limit, it is clear, when those claims are read in light of the specification (page 10, lines 4 et seq.) that:

"... the physical and biochemical properties of polynucleotides containing small numbers of probe substituents should not be significantly altered so that current procedures using radioactive nucleotides probes need not be extensively modified."

Each of the nucleotides in an oligo or polynucleotide may be modified; if the nucleotide is monomeric then "at least

one" is equivalent to "all". The purpose of the invention is to provide a detectable product which forms only in certain circumstances. The most efficient method would be to use only that minimal number of modified nucleotides that is consistent with obtaining a detectable product. Nevertheless, there is nothing inherent in the invention that would preclude one from modifying all the nucleotides, if one so chose, provided only that the preferred functional limitation set forth in the specification is observed.

The Examiner asserts that in claims 101 and 110 "the last three lines of said claim[s] as amended in amendment B imply a multi-layered immunological sandwich(es) which is/are not described in enough detail for one of ordinary skill to know the metes and bounds of what is being claimed." This assertion is without merit.

As of the filing date of this application, immunological sandwiches were known in the art, as referenced in the specification at page 35, lines 28 et seq. The usefulness of this technique in the present invention is described with examples at the point in the specification.

The Examiner contends that in claims 103 and 112 "the terms 'fluorescent dye', 'electron dense protein'[and] 'enzyme capable of producing a detectable reaction product' amount to functional language so broad and indefinite as to be useless in determinations of the metes and bounds of what is being claimed." Applicants traverse this contention.

The meaning of each of the objected to terms were so well known to those skilled in the art at the filing date of this application that there can be no dispute as to their meaning. In addition to employing such commonly recognized terms, applicants further indicate the meaning of the terms by

providing illustrative examples. At page 2, lines 9 et seq. fluorescent dyes are exemplified by fluorescein and rhodamine, electron-dense reagents by ferritin, hemocyanin or colloidal gold and enzymes capable of producing a detectable reaction product by peroxidase or alkaline phosphatase. Accordingly, those terms are neither broad nor indefinite.

The Examiner contends that in claims 138 and 139 "the subject matter claimed is expanded further to include both 2',3'- and 3',5'-cyclic monophosphates, neither of which is represented by even a single specific embodiment." This contention should be withdrawn.

Applicants refer the Examiner to the specification, at page 40, lines 9 et seq. for the basis for the cyclic monophosphate embodiment of the present invention. Since the phosphate can be attached only at the x, y, or z positions, corresponding to the 2, 3, or 5 positions, applicants' disclosure of the generalized structure of the claimed compositions, especially when coupled with a statement of their intended uses, is sufficient to disclose the subject matter of claims 138 and 139 to a skilled practitioner in the art.

The Examiner asserts that in claims 146-148 "the terms 'A is a ligand' and dependent references thereto are both indefinite and unenabled in view of one of ordinary skill's inability to determine which 'ligand[s]\' applicant intend to claim." Applicants traverse this assertion.

Applicants intend to claim all ligands that meet the criteria set forth in the specification which, at page 12, lines 1 et seq., defines "A" in functional terms. The following paragraph provides support for that claim when it states "A may therefore be any ligand which possess these properties ...".

The Examiner also contends that in claim 151 "the terms 'enzyme' and 'substrate' are both indefinite and unenabled in view of one of ordinary skill's inability to determine the metes and bounds of the subject matter applicant intends to claim." This contention should be withdrawn.

The meaning of the terms "enzyme" and "substrate" were so well known to those skilled in the art at the time of the filing of this application that there can be no dispute as to their meaning. See, e.g., The Condensed Chemical Dictionary Eighth ed., p. 348 (enclosed as Exhibit A). Enzymes, the catalysts of biological systems, are highly specific both in the reaction catalyzed and in their choice of reactants, which are called substrates. These terms are employed throughout this application for their ordinary scientific meaning.

Claim 101 stands rejected under 35 U.S.C § 112, second paragraph, as "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention." In particular, the Examiner asserts "the term 'N<sup>1</sup> position' (see p. 2, line 4 of amendment B) is incorrect, i.e. the sugar moiety has no nitrogen atoms. It appears that applicant intended -- N<sup>1</sup> position --." Applicants have obviated this rejection by amending claim 101 by substituting " N<sup>1</sup> position" in place of "N<sup>1</sup>".

The Examiner contends that claims 101 and 110 "appear to be substantial duplicates." Applicants traverse this contention.

Claim 101 recites a mononucleotide having a specific structure. Claim 110 recites an oligo or polynucleotide containing modified nucleotides according to claim 101. Thus, claim 101 is not a "substantial duplicate" of claim 110.



Finally, the Examiner asserts that applicants' attorney, James F. Haley, Jr. is not an attorney of record in this case. The Examiner is mistaken.

The present application is a divisional of United States patent application 496,915, filed May 23, 1983. Mr. Haley was named attorney of record in the '915 application in a Power of Attorney executed on September 11, 1984 by the Assignee of record in that application. Applicants have enclosed, as Exhibit B hereto, a copy of that Power of Attorney in the prior application which appoints Mr. Haley as an attorney of record.

Applicants request that the Examiner consider the foregoing remarks and allow the claims of this application as.

Respectfully submitted,

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I Hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on December 20, 1990

*Teresa Solomon*  
Name of Person Signing Certificate

*Teresa Solomon*  
Signature of Person Signing Certificate

12/20/90  
Date of Signature

Exhibit A

*The*  
*Condensed Chemical*  
*Dictionary*

EIGHTH EDITION

*Revised by*

*GESSNER G. HAWLEY*

*Formerly Executive Editor, Reinhold Publishing Corporation*  
*Coeditor, Encyclopedia of Chemistry*



VAN NOSTRAND REINHOLD COMPANY

NEW YORK CINCINNATI TORONTO LONDON MELBOURNE

**energy.** Physicists define energy as the capacity for doing work. Perhaps its most direct application to chemistry is in the formation and decomposition of chemical compounds. For example, in the synthesis of carbohydrates from carbon dioxide and water by radiant energy, the energy input is exactly balanced by the heat of decomposition (combustion, rotting). This exemplifies the law of conservation of energy, which states that energy cannot be manufactured or destroyed, but only transferred from one point to another, or transformed from one state to another, as in nuclear fission. The latter yields 200 million electron volts for each uranium atom, whereas the rupture of a carbon-hydrogen bond yields only 5 electron volts.

Free energy is a thermodynamic function; in chemical reactions it is a measure of the extent to which a substance can react. Kinetic energy (the energy of motion) is most clearly exhibited in gases and liquids, in which molecules have much greater freedom of movement than in solids. Energy is probably the most all-embracing entity in the universe. Mass is convertible into energy according to Einstein's equivalence equation  $E = mc^2$ . Electrons, photons, and other so-called fundamental particles are actually bundles of energetic concentration in various stages of excitation. See also nuclear energy; photosynthesis; carbon cycle (1).

**enfleurage.** Extraction of odoriferous components of flowers by means of fats or mixtures of fat and talow, the process being carried out at room temperature to avoid decomposition of the desired perfumes. The latter are separated from the fat by washing with alcohol. See also essential oil; perfume.

**engine distillate.** A petroleum distillate similar to naphtha but often of higher distillation range.

**"Engravoclor."**<sup>110</sup> Trademark for ferric chloride solution specially prepared for photo-engraving process. Contains 43% ferric chloride.

**"Enide."**<sup>111</sup> Trademark for selective agricultural herbicide, N,N-dimethyl-2,2-diphenylacetamide. Hazard: Moderate to high toxicity.

**"Enjay Butyl HT Series Rubber."**<sup>112</sup> Trademark for isobutylene rubber containing chlorine; both chlorine and unsaturation are present in such a way that each may be utilized in vulcanization. Compatible with most other elastomers. The outstanding property of this polymer is its ability to resist heat up to 400° F.

**"Enjay Butyl Latex."**<sup>113</sup> Trademark for isobutylene type rubber in aqueous emulsion.

**"Enjay Butyl Rubber."**<sup>114</sup> Trademark for isobutylene type rubber. A copolymer of isobutylene with a small proportion of isoprene to give a controlled, low degree of unsaturation. Processing is similar to that of natural rubber except that no premastication is required.

**"Enjay EPR."**<sup>115</sup> Trademark for a rubber raw material that is an amorphous, saturated copolymer of ethylene and propylene.

**"Enjay EPT."**<sup>116</sup> Trademark for a rubber raw material that is an elastomeric, amorphous terpolymer of ethylene, propylene, and a small quantity of a non-conjugated diene.

**"Enjay Liquid Rubber."**<sup>117</sup> Trademark for a low molecular weight butyl rubber in semiliquid or liquid form suitable for coatings, sealants, adhesives, etc.

**"Enjay."**<sup>118</sup> Trademark of several special grades of asphalt.

**enol.** A chemical grouping containing both a double bond (ene) and a hydroxyl group (OH), forming an intermediate and reversible product. Enols are characteristic of racemic compounds (q.v.).

**enolase.** An enzyme active in glycolysis which catalyzes the conversion of 2-phosphoglyceric acid to the phosphorylated enol form of pyruvic acid.

**"Enovid."**<sup>119</sup> Trademark for norethynodrel with mestranol. Oral contraceptive approved by FDA.

**"Enplate."**<sup>120</sup> Electroless plating processes for depositing metallic films on plastics, other non-conductors, and metals by chemical reduction.

**"Enstrip."**<sup>121</sup> Trademark for various solutions designed for stripping selectively one metal from another. Most types are supplied as powders that are added to water for use.

**enterokinase.** An enzyme found in the small intestine which converts trypsinogen into trypsin.

**"Enth-Acid."**<sup>122</sup> Trademark for a blend of acid salts, activators and surfactants which can be used as a replacement for liquid acids. Used for acid dipping of iron, steel, brass, copper, or zinc die castings prior to plating.

**"Enthol."**<sup>123</sup> Trademark for phosphoric acid-solvent mixtures designed for degreasing and oxide removal for such metals as steel, aluminum, and zinc. Materials are supplied in the liquid form.

**"Enthonite."**<sup>124</sup> Trademark for a polyvinyl plastisol coating used for coating metals; primarily for imparting resistance to acid, alkaline, and electroplating solutions. Contains 100% solids and is applied by dipping.

**"Enthox."**<sup>125</sup> Trademark for salts that are added to water for producing chromate coatings on zinc and cadmium to withstand 100 or more hours in 20% salt spray.

**"Entodon."**<sup>126</sup> Trademark for propiodal (q.v.).

**entrainer.** An additive for liquid mixtures that are difficult to separate by ordinary distillation. The entrainer usually forms an azeotrope with one of the compounds of the mixture and thereby aids in the separation of such a compound from the remainder of the mixture.

**environmental chemistry.** That aspect of chemistry associated with water pollution and purification, air pollution, and waste disposal of various types (solid, liquid, gaseous, and radioactive). See also eutrophication; biodegradability; smog; waste, industrial; ecology.

**"Enzose."**<sup>127</sup> Trademark for a liquid carbohydrate in two grades with dextrose equivalent (D.E.) of 72 or 87 and pH of 3.8-4.4 or 4.0-5.0. Shipped in tank cars.

Uses: Chemicals, colorants; drugs, pharmaceuticals.

**enzyme.** One of a group of complex organic substances formed in the living cells of plants and animals; they are necessary catalysts for the chemical reactions of biological process e.g., pepsin catalyzes digestion. The first synthesis of an enzyme was reported in 1969 (ribonuclease). Enzymes are very specific in their catalytic behavior; a given enzyme is effective for only one particular reaction. Enzymes are often classified by the kind of substance (substrate) consumed in the reactions catalyzed. For

*Exhibit B*

Art Unit : 123  
 Applicants : David C. Ward et al.  
 Serial No. : 496,915  
 Filed : May 23, 1983  
 For : MODIFIED NUCLEOTIDES AND METHODS OF  
 PREPARING AND USING SAME

Hon. Commissioner of Patents  
 and Trademarks  
 Washington, D.C. 20231

REVOCATION OF POWER OF ATTORNEY  
 and  
POWER OF ATTORNEY

Sir:

YALE UNIVERSITY, a State of Connecticut non-profit corporation located in New Haven, Connecticut, the assignee of the entire right, title and interest in the above-identified continuation application by Assignment, recorded on February 24, 1982, on Reel 3950, Frame 0423, in patent application 255,223, filed April 17, 1981, hereby revokes all Powers and Associate Powers of Attorney heretofor existing in the above-identified patent application.

YALE UNIVERSITY hereby appoints the following attorneys as its principal attorneys of record to prosecute this application and to transact all business in the United States Patent and Trademark Office in connection therewith:

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YALE UNIVERSITY

DATED: September 11, 1984

By: JW B

John W. Buckman

Title:

Vice President for Finance